

PATENT SPECIFICATION

(11) 1 367 203

1 367 203

- (21) Application No. 685/72 (22) Filed 6 Jan. 1972
 (31) Convention Application No. 7 100 283 (32) Filed 7 Jan. 1971 in (19)
 (33) France (FR)
 (44) Complete Specification published 18 Sept. 1974
 (51) International Classification C07D 5/30; A61K 27/00; C07D 99/02//C07C 125/06; C07D 63/12
 (52) Index at acceptance

C2C 1340 1470 1510 200 215 220 226 227 22Y 247 250
 251 253 254 25Y 28X 30Y 327 332 340 342 34Y
 351 354 360 361 365 366 368 36Y 584 590 594
 595 599 602 604 625 627 628 62X 635 63X
 652 657 658 65X 662 70Y 742 790 79Y KA KB
 KK KM KN KR KS KY ME



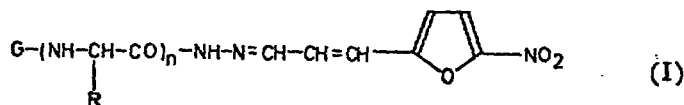
(54) NOVEL SUBSTITUTED (NITROFURYLACRYLIDENE)-HYDRAZINES AND COMPOSITIONS CONTAINING THEM

(71) We, LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE, a French Body Corporate, of 115 Avenue Lacassagne, 69, Lyon 3, Rhone, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel substituted (nitrofurylacrylidene)-hydrazines, to a process for their preparation and to pharmaceutical and veterinary compositions containing them.

Certain nitrofuran derivatives are known and used both in pharmacy and in the veterinary field, especially the compounds N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidone, which has the B.P. approved name furazolidone, and N-(5-nitro-2-furfurylidene)-1-aminohydantoin, which has the B.P. approved name nitrofurantoin. These compounds, when used in pharmacy, do however possess disadvantages, and in particular they have an emetic effect. In contrast, nitrofuran derivatives of the invention, as well as having an appreciable antibacterial activity for a toxicity of the same order as that of furazolidone and decidedly lower than that of nitrofurantoin have been found to have the very great advantage of not being emetic.

The nitrofuran derivatives with which the invention is concerned are the substituted (nitrofurylacrylidene)-hydrazines represented by the general formula:

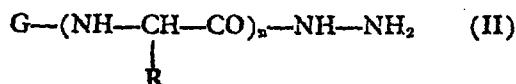


in which $n=1$ or 0 ;

G is a furoyl, thenoyl, nitrothenoyl or carbobenzyloxy radical; and

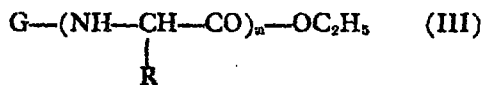
R is hydrogen or a methyl, butyl, isobutyl, hydroxymethyl, benzyl, *p*-hydroxybenzyl or δ -(2-furoyl)-aminobutyl radical.

It is possible to obtain these novel hydrazines by reaction of 5-nitro-2-furyl acrolein with a hydrazide which is represented by the formula



in which n , G and R have the same meanings as in formula I. The reaction can be effected by hot condensation in organic solvent medium.

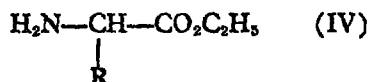
The hydrazides of formula II can be obtained by reacting hydrazine with an amino ester of the general formula:



in which n and G have the same meanings as in formula I.

The process can be effected in the presence of a catalytic quantity of acid, such as acetic acid.

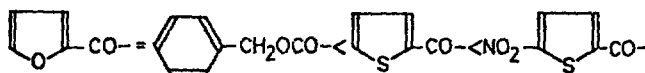
The amino esters of formula III in which n is 1 can be obtained by reacting an amino ester of formula



with an acid chloride of formula $\text{G}-\text{Cl}$, in which G and R have the same meanings as in formula I, in the presence of an alkali agent. The alkali agent can be mineral or organic, for example the acid carbonate of sodium, triethylamine, or pyridine.

The novel (nitrofurylacrylidene) hydrazines are distinguished by their ability to inhibit the growth of bacteria. This effect extends to gram-positive and gram-negative organisms.

Biological research has made apparent the importance of the nature of the protective group G of the general formula I. The effect of these groups can be classed in the following order.



Since it has been established to be advantageous to select the heterocyclic carrier of the NO_2 -group participating in the formation of the Schiff base from the family of furans and thiophenes, the biological activity being completely lost when they are replaced by the isostere: pyrrole, the $[\text{N}^1-(5'-\text{nitro}-2'-\text{thenoyl})-\text{N}^2-(5''-\text{nitro}-2''-\text{furyl}-\text{acrylidene})]$ - hydrazine and $[\text{N}^1-(5'-\text{nitro}-2'-\text{thenoyl glycy})-\text{N}^2-(5''-\text{nitro}-2''-\text{furyl acrylidene})]$ hydrazine form particularly outstanding active principles.

These two products have an activity "in vitro" which is identical with that of furazolidone for an equal toxicity. In addition, a particularly important fact is that these active principles are free from any emetic effect on dogs, even in a strong dose.

The medicaments of the invention have low toxicity, the strongest dose tolerated by mice by oral route being at least 3200 mg/kg.

The results of pharmacological tests are set out in the following tables I and II.

In table I, the control substance is furazolidone and in table II it is nitrofurantoin.

The antibacterial coefficients have been determined in vitro in the majority of cases on specific E. COLI strains.

TABLE I

Example	Antibacterial coefficient	LD 50-kg perorally mice
Control	100	
Ex. 1	0	
Ex. 2	106	3,200 mg
Ex. 3	115	>3,200 mg
Ex. 4	120 in vitro 73 in vivo	>3,200 mg
Ex. 5	175	>3,200 mg
Ex. 7	58	>3,200 mg
Ex. 8	75	>3,200 mg
Ex. 9	118	>3,200 mg
Ex. 10	97	>3,200 mg
Ex. 12	120	>3,200 mg
Ex. 13	113	>3,200 mg
Ex. 14	94	>3,200 mg
Ex. 15	>100 on gram-positive germs	>3,200 mg
Ex. 16	95	3,200 mg

TABLE II

	Example	Antibacterial coefficient	LD 50-kg perorally mice	
	Control	100		
	Ex. 6	115	>3,200 mg	
5	Ex. 11	140	3,200 mg	5

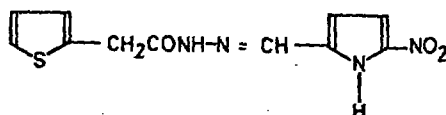
The daily dose sufficient to obtain the desired therapeutic effect on a human being varies from approximately 10 to 500 mg.

The compounds of the invention are normally administered in the form of a pharmaceutical composition comprising a compound of formula I in association with a pharmaceutical carrier or excipient therefor. The composition is advantageously made up in a dosage unit form appropriate to the desired mode of administration, which may be oral or topical. For example the composition may be in the form of a powder, suspension, ointment or tablet.

Examples illustrating the invention in a non-limiting manner are given below, with the exception of Example 1 which describes the preparation of a comparison compound referred to in Table I above.

Example 1.

N^1 -[N' -2'-furoyl ($\pm$) alanyl]- N^2 -[5''nitro-2''furyl-acrylidene]-hydrazine:



$C_{11}H_{10}N_4O_3S$

$M = 278.28$

3.9 g ($\frac{\text{mol}}{40}$) of (2-thienyl acetyl) hydrazide are dissolved in 32 ml of methanol, whereafter 3.5 g ($\frac{\text{mol}}{40}$) of 5-nitro-2-pyrrol aldehyde in 35 ml of tetrahydrofuran are added. Heating under reflux takes place for 5 hours. After cooling, adding ether and then cooling in the refrigerator, there are obtained:

1st cut: 3.6 g—yellow $M_p = 188-190^\circ \text{C.}$
2nd cut: 1.7 g—yellow $M_p = 190-192^\circ \text{C.}$

The yield is 5.3 g, i.e. 76% (theoretical yield=6.95 g).

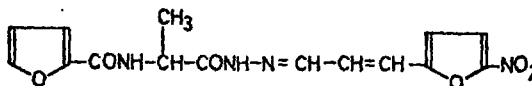
The 1st cut, after being recrystallised twice from isopropanol and dried at 50°C. under strong vacuum, melts at $192-194^\circ \text{C.}$

Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	47.46	3.62	20.13	11.52
Found:	47.37	3.65	19.92	11.66

Example 2.

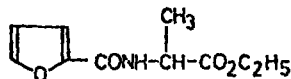
N^1 -[N' -2'-furoyl ($\pm$) alanyl]- N^2 -[5''nitro-2''furyl-acrylidene]-hydrazine:



$C_{15}H_{14}N_4O_6$

$M = 346.29$

a) N^1 -2 furoyl ($\pm$) alanine ethyl ester:



$C_{10}H_{13}NO_4$

$M = 211.20$

23.4 g ($\frac{\text{mol}}{5}$) of ($\pm$) alanine ethyl ester are dissolved in 100 ml of dry benzene.

20.3 g ($\frac{\text{mol}}{5}$) = 20.22 g of triethylamine are added, followed by dropwise addition of

26.1 g ($\frac{\text{mol}}{5}$) of furoyl chloride. The temperature is raised from 22 to 35° C. and there is a precipitation of crystals of



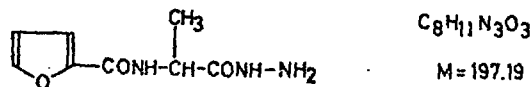
After suction-filtering, washing with water and drying, and also evaporation of the solvent, there is obtained a quantitative yield of 42.2 g of product of Mp=68—71° C. After being recrystallised twice (diisopropylether) the melting point is 72—73° C.

Gravimetric analysis:

	C%	H%	N%
Calculated:	56.85	6.20	6.63
Found:	56.83	6.19	6.58

10

b) N¹-[N'-2'-furoyl ($\pm$) alanyl]-hydrazide:



15 21.1 g ($\frac{\text{mol}}{10}$) of N-furoyl ($\pm$) alanine ethyl ester, 20.2 g ($\frac{\text{mol}}{2.5}$) = 20 g of

NH₂—NH₂ . 98% H₂O and 0.5 ml of acetic acid are heated under reflux for 5 hours.

After evaporation to dryness, the oily residue which is obtained is dispersed under ether and this is solidified. A white product of Mp=115—120° C. is obtained with a quantitative yield, this product melting at 132—133° C. after being recrystallised twice from isopropanol.

Gravimetric analysis:

	C%	H%	N%
Calculated:	48.72	5.62	21.31
Found:	48.61	5.77	21.17

20

25 c) N₁-[N'-2-furoyl ($\pm$) alanyl]-N²-[5''-nitro-2''-furyl acrylidene]-hydrazine:

10 g ($\frac{\text{mol}}{20}$) = 9.85 g of N¹-[N'-furoyl ($\pm$) alanyl]-hydrazide, in 120 ml of

methanol, and 8.4 g ($\frac{\text{mol}}{20}$) = 8.35 g of 5-nitro-2-furyl acrolein, in 63 ml of tetrahydro-

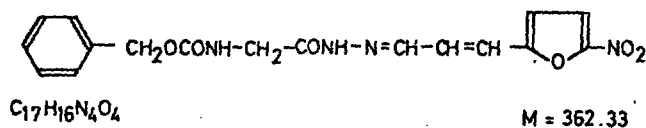
furan, are heated together under reflux for one hour. After concentration to half volume, cooling in a refrigerator, suction-filtering, washing with isopropanol and then with ether, 11.8 g of product are obtained with a yield of 80.5% (theoretical yield = 14.65 g), the product having a melting point of 192—195° C. (with decomposition). After recrystallisation from acetone, the melting point is 197.5—198.5° C. with decomposition.

Gravimetric analysis:

	C%	H%	N%
Calculated:	52.02	4.07	16.18
Found:	51.96	4.13	16.07

35

Example 3.
 N^1 -[N' -carbobenzoxyglycyl]- N^2 -[5'-nitro-2'-furylacrylidene]-hydrazine:



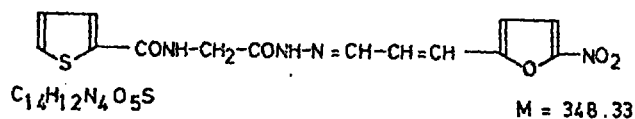
7 g ($\frac{\text{mol}}{31.8}$) of N^1 -[N' -carbobenzoxyglycyl]-hydrazide are dissolved at ambient tem-

perature in 80 ml of methanol. There are then added dropwise 5.3 g ($\frac{\text{mol}}{31.8}$) of 5-nitro-2-furyl acrolein in 53 ml of tetrahydrofuran. Heating under reflux takes place for one hour, followed by concentration to half volume. Crystals are produced which are suction-filtered and washed with ether. There are obtained 8.7 g of crystals melting at 159—160° C., with a yield of 74.2% (theoretical yield=11.7 g). After recrystallisation (methanol), the melting point is unchanged.

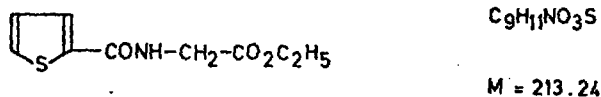
Gravimetric analysis:

	C%	H%	N%
Calculated:	54.83	4.33	15.04
Found:	54.92	4.38	15.06

Example 4.
 N^1 -[N' -2'-thenoylglycyl]- N^2 -[5''nitro-2''furyl acrylidene]-hydrazine:



a) Ethyl-N-thenoyl-2-glycocolate:



Method A—

To 14.2 g ($\frac{\text{mol}}{7.25}$) of ethyl glycocolate in solution in 70 ml of pyridine are added dropwise 20.2 g ($\frac{\text{mol}}{7.25}$) of 2-thiophene carboxylic acid chloride. Agitation takes place for one hour at ambient temperature and then the mixture is poured into iced water. Suction-filtering yields a 1st cut: 19.4 g coloured, $M_p = 86$ — 88° C. The mother liquors extracted with ethyl acetate, yield a second cut: 6 g coloured, $M_p = 86$ — 88° C. Yield: 25.4 g=86.4% (theoretical yield=29.4 g).

Method B—

To a solution of 21.1 g ($\frac{\text{mol}}{6.6}$) of ethyl glycocolate hydrochloride, in 150 ml of water, containing 25.3 g ($\frac{\text{mol}}{3.3}$) of $NaHCO_3$, there are simultaneously added while

stirring well: 24.1 g ($\frac{\text{mol}}{6.6}$) of 2-thiophene carboxylic acid chloride and 38 ml of an

aqueous solution containing 12.7 g ($\frac{\text{mol}}{6.6}$) of NaHCO_3 . The time taken for the addition is 15 minutes. Heating at 50°C . takes place for one hour. The solid is precipitated on completing the addition. After suction-filtering, washing with water, there are obtained 25.5 g=79% (theoretical yield: 32.2 g) of coloured product, $\text{Mp}=88-90^\circ \text{C}$.

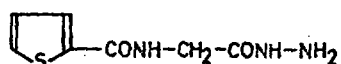
After recrystallisation, (diisopropyl ether+ethyl acetate), a white product of $\text{Mp}=90-90.5^\circ \text{C}$. is obtained.

Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	50.70	5.20	6.57	15.04
Found:	50.72	5.23	6.54	14.99

— νNH	3,400 cm^{-1}
— $\nu\text{CH}=\text{CH}$ (thiophene)	3,120 cm^{-1}
— νCO (ester)	1,740 cm^{-1}
— νCO (conjugated amide)	1,650 cm^{-1}

b) N^1 -[N' -2'-thenoylglycyl]-hydrazide:



$$M = 199.22$$

21.3 g ($\frac{\text{mol}}{10}$) of ethyl N-2-thenoyl glycolate, 20 g ($\frac{\text{mol}}{2.5}$) of 98% hydrazine, 30 ml of isopropanol and 0.4 ml of acetic acid are mixed. Heat is produced, followed by crystallisation. The crystals are left at ambient temperature for a few hours and then in a refrigerator. After suction-filtering, washing with ether, there are obtained: 19.3 g=97% (theoretical yield: 19.9 g) of solid melting at $176-177^\circ \text{C}$. After recrystallisation (water) and drying at 100°C . under vacuum, $\text{Mp}=178-179^\circ \text{C}$.

Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	42.20	4.53	21.10	16.10
Found:	42.29	4.60	21.05	16.16

— νNH	3,300 cm^{-1}
— νCO (conjugated)	1,630—1,650 cm^{-1}
— νCO	1,670 cm^{-1}
— $\nu\text{CH}=\text{CH}$ (thiophene)	3,080 cm^{-1}
— $\nu\text{C}=\text{C}$ (thiophene)	885 cm^{-1} —1,030 cm^{-1} — 1,060 cm^{-1}

c) N^1 -[N' -2'-thenonylglycyl]- N^2 -(5''-nitro-2''-furylacrylidene)-hydrazine:

8 g ($\frac{\text{mol}}{25}$) of N^1 -[N' -2'-thenonylglycyl]-hydrazide are dissolved at

60°C . in 200 ml of ethylene glycol. At a temperature of 50°C ., 6.8 g ($\frac{\text{mol}}{25}$)

of 5-nitro-2-furyl acolein in 68 ml of tetrahydrofuran are introduced. Crystallisation is produced a few minutes after the addition. Heating takes place at 50°C . for 30 minutes. After suction-filtering and washing with ether, there are isolated 13.8 g of solid with a melting point of $233-234^\circ \text{C}$. (with decomposition) and with a yield

of 99.3% (theoretical yield=13.9 g). After recrystallisation from a mixture of dimethyl formamide and ether, the melting point is 233° C. (with decomposition).

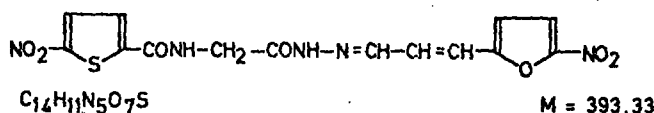
Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	48.27	3.47	16.08	9.20
Found:	48.19	3.43	15.98	9.30

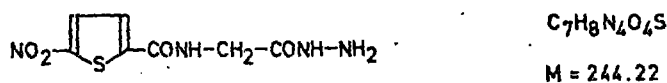
— νNH	3,380 cm ⁻¹
— νCO	1,690 cm ⁻¹
— νCO conjugated	1,645 cm ⁻¹
— νC—NO ₂	1,510 and 1,550 cm ⁻¹
— ν 	1,020 cm ⁻¹

Example 5.

N¹-[5'-nitro-2'-thenoylglycyl]-N²-[5''-nitro-2''-furyl acrylidene]-hydrazine:



a) N¹-[5'-nitro-2'-thenoylglycyl]-hydrazide:



21.2 g ($\frac{\text{mol}}{12.15}$) of ethyl 5-nitro-2-thienoyl glycolate are dissolved in 480 ml of methanol and the solution has added thereto very slowly, at a temperature of 5° C., 12.8 g ($\frac{\text{mol}}{4} = 12.5$ g) of NH₂—NH₂ · 98% H₂O in 40 ml of methanol. The mixture is cooled to 0° C. and agitation is continued for 2 hours at this temperature. 45 minutes after the commencement of the cooling, crystallisation occurs. After suction-filtering (difficult) in the presence of ether, there are obtained:

1st cut: 11.5 g, yellow, Mp=186—187° C.
2nd cut: 4.8 g, yellow, Mp=189.5—190° C. The yield is 16.3 g=80.5% (theoretical yield: 20 g).
After being recrystallised twice (water), Mp=190.5—191° C.

Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	34.42	3.30	22.94	13.13
Found:	34.55	3.34	22.90	13.25

— νNH	3,300 cm ⁻¹
— νCO	1,680 cm ⁻¹
— νCO conjugated	1,640 cm ⁻¹
— νNO ₂	1,580 cm ⁻¹

b) N¹-[5'-nitro-2'-thenoylglycyl]-N²-[5''-nitro-2''-furylacrylidene]-hydrazine:

At a temperature of 60° C., 6.1 g ($\frac{\text{mol}}{40}$) of N¹-[5'-nitro-2'-thenoylglycyl]-hydrazide

are dissolved in 200 ml of ethylene glycol. At the same temperature, 4.2 g ($\frac{\text{mol}}{40}$)

of 5-nitro-2-furyl acrolein in 42 ml of tetrahydrofuran are introduced into the solution. Heating takes place for one hour at 60° C. A precipitation of red crystals is observed after cooling. (In certain cases, after heating for half an hour). After filtering with suction and washing with water, there are obtained 8.1 g, yield=82.6% (theoretical yield: 9.84 g) of an orange product, Mp=217—218° C.

After recrystallisation (8.1 g in 875 ml of ethyl acetate) and drying to constant weight at 140° C. under a strong vacuum, the melting point is 222—224° C. (with decomposition).

Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	42.76	2.81	17.81	8.15
Found:	42.70	3.04	17.78	8.09

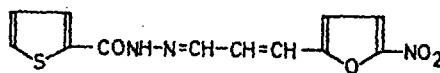
— νCO	{ 1,720 cm^{-1} 1,650 cm^{-1}	(CO of the enolised hydrazide-conjugated CO OH C=N—)
— νNO_2	1,550 cm^{-1}	
— C—N	1,370 cm^{-1}	
— νNH	3,250 cm^{-1}	

— ν 	3,100 cm^{-1}
---	------------------------

— ν 	3,150 cm^{-1}
---	------------------------

Example 6.

N¹-[2'-thenoyl]-N²-[5''nitro-2''-furylacrylidene]-hydrazine:



C₁₂H₉N₃O₄S

M = 291.27

14.2 g ($\frac{\text{mol}}{10}$) of N¹-(2'-thenoyl)-hydrazide in crude form are dissolved in 140

ml of methanol. 16.7 g ($\frac{\text{mol}}{10}$) of 5-nitro-2-furyl acrolein in 167 ml of tetrahydrofuran are added dropwise thereto. The solution is heated under reflux for one hour. Crystallisation is observed 5 minutes after completing the addition. After cooling, there is obtained a first cut of 16.9 g of yellow crystals, Mp=219—220° C. (with decomposition).

After concentrating the mother liquors, there are obtained a second cut of 1.1 g (yellow) Mp=219—220° C. (with decomposition) and a third cut of 3.5 g (brown) of Mp=212—213° C. (with decomposition). Yield: 21.5 g=72.6% (theoretical yield: 29.1 g).

After recrystallisation (alcohol+dimethyl formamide at 80° C.), Mp=219—220° C. (with decomposition).

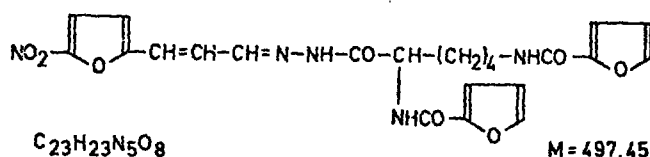
Gravimetric analysis:

	C%	H%	N%	S%
Calculated:	49.48	3.11	14.43	11.01
Found:	49.50	3.14	14.36	11.12

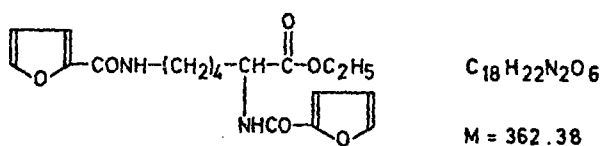
— νNH	3,280 cm^{-1}
— νNO_2	1,540 cm^{-1}
— νCO (conjugated)	1,650 cm^{-1}

Example 7.

N^1 -[5'-nitro-2'-furylacrylidene]- N^2 -[N^{α},N^{ϵ} -2''-difuroyl- $\pm$ lysyl]-hydrazine:



a) N^{α},N^{ϵ} -2'-difuroyl lysine ethyl ester:



24.7 g ($\frac{\text{mol}}{10}$) of lysine dihydrochloride ethyl ester are dissolved in 200 ml of water containing 25.4 g ($\frac{\text{mol}}{3.3}$) of NaHCO_3 . While stirring vigorously, there are simultaneously added: 26 g ($\frac{\text{mol}}{5}$) of furoyl chloride and 50 ml of an aqueous solution of 16.8 g ($\frac{\text{mol}}{5}$) of NaHCO_3 . The addition lasts 20 minutes. Heating to 50° C. takes place for one hour, followed by extraction with ethyl acetate and evaporation to dryness, the oily residue which is obtained slowly solidifying. The yield is 22.9 g = 63% (theoretical yield: 36.2 g) as a white solid of $M_p = 101-102^\circ \text{C}$.

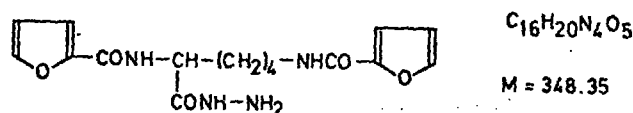
Analysis:

	C%	H%	N%
Calculated:	59.65	6.12	7.73
Found:	59.70	6.16	7.85

— νNH (large)	3,300 cm^{-1}
— νCO ester	1,740 cm^{-1}
— νCO amide	1,650 cm^{-1}
— $\nu\text{CH}=\text{CH}$ (furan)	3,060—3,120 cm^{-1}

— ν	1,020—1,080 cm^{-1}
---------	------------------------------

b) N^1 -[N^{α},N^{ϵ} -2'-difuroyl ($\pm$) lysyl]-hydrazide:



16.1 g ($\frac{\text{mol}}{20}$) of N^{α},N^{ϵ} -2'-difuroyl ($\pm$) lysine ethyl ester, in solution in isopropanol, 10.2 g ($\frac{\text{mol}}{5} = 10 \text{ g}$) of $\text{NH}_2\text{-NH}_2$, 98% H_2O and 0.5 cc of acetic acid are heated for 5 hours. The solution is evaporated to dryness and the residue is dispersed under ether, and there are obtained 16 g, yield = 92% (theoretical yield 17.35 g) of a white product melting at 155—158° C. After recrystallisation (ethanol), the melting point = 161—162° C.

Analysis:

	C%	H%	N%
Calculated:	55.17	5.78	16.08
Found:	55.12	5.80	16.04

5	— νNH	3,350 cm ⁻¹	5
	— νCO (large)	1,630—1,670 cm ⁻¹	
	— νCH ₂	2,950 cm ⁻¹	

c) N¹-[5-nitro-2'-furylacrylidene]-N²-[N^α,N^α-2''-difuroyl (±) lysyl]-hydrazine:

In accordance with the conditions of Example 3, starting with 8.7 g ($\frac{\text{mol}}{40}$)

of N¹-[N^α,N^α-2'-difuroyl (±) lysyl] hydrazide, in 80 ml of methanol, there are obtained 11.6 g=93% (theoretical yield: 12.45 g) of a solid having an Mp=205—210° C. After recrystallisation (tepid dimethyl formamide+ether), Mp=212—213° C.

This product probably exists in two forms, because after the first recrystallisation, the melting point falls to 179—180° C. By recrystallising this latter product under the same conditions, a melting point=212—213° C. is reached.

Analysis:

	C%	H%	N%
Calculated:	55.52	4.66	14.08
Found:	55.45	4.63	14.17

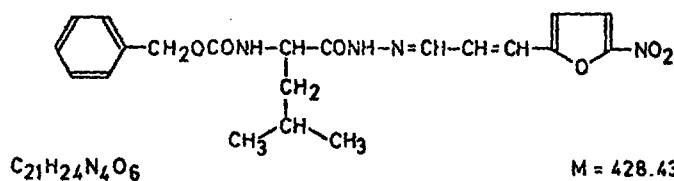
20	— νNH	3,380 cm ⁻¹	20
	— νCH ₂	2,940 cm ⁻¹	
	— νHC=CH 	3,120 cm ⁻¹ —1,020 cm ⁻¹	

	— νCO (enolised hydrazide)	1,700 cm ⁻¹	15
	 —C=N)	1,650 cm ⁻¹ (conjugated)	

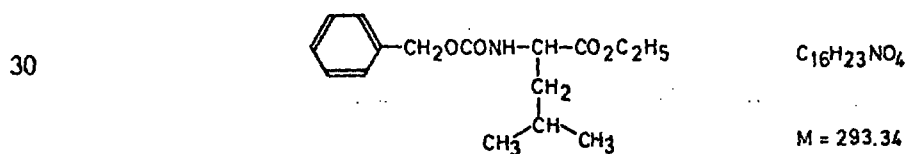
25	— νNO ₂	1,550 cm ⁻¹	25
----	--------------------	------------------------	----

Example 8.

N¹-[carbobenzoxy (±) leucyl]-N²-[5-nitro-2'-furylacrylidene]-hydrazine:



a) N-(±) carbobenzoxy (±) leucine ethyl ester:



At about 0°, 39.1 g ($\frac{\text{mol}}{5}$) of (±) leucine ethyl ester hydrochloride are dissolved in 100 ml of water containing 33.5 g ($\frac{\text{mol}}{2.5}$) of NaHCO₃. There are simultaneously

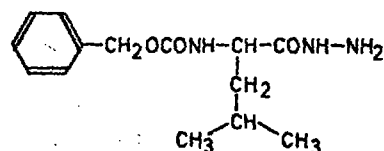
added 34 g ($\frac{\text{mol}}{5}$) of carbobenzoxy chloride and 50 ml of an aqueous solution of 16.7

g ($\frac{\text{mol}}{5}$) of NaHCO_3 . On completing the addition, stirring is continued for 10 minutes at ambient temperature. The oil which forms is extracted with ether and distilled. The yield is 37.3 g = 63.6% (theoretical yield: 58.6 g) of a yellow oily product. Boiling point $0.37-0.4 = 138-139.5^\circ \text{C}$.

Chromatography in vapour phase reveals the presence of 20% of volatile impurities.

— νNH 3,350 cm^{-1}
— νCO (large) 1,730 cm^{-1}

b) N-carbenzoxy ($\pm$) leucyl hydrazide:



$\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_3$

$M = 279.33$

29.3 g ($\frac{\text{mol}}{10}$) of N-carbenzoxy ($\pm$) leucine ethyl ester, 320 ml of ethanol,

20.4 g ($\frac{\text{mol}}{2.5} = 20$ g) of 98% hydrazine hydrate and 0.5 ml of acetic acid are left at ambient temperature for 48 hours and then evaporated to dryness. The residue is washed with water and extracted with ether. After evaporation of the ether, an oil is left which is dried under strong vacuum. The yield is 12.3 g = 44.2% (theoretical yield: 27.9 g) of a product which melts at $104-105^\circ \text{C}$. After recrystallisation (propylene oxide-heptane [2:1]), $Mp = 105-108^\circ \text{C}$.

This product is not analytically pure and it is used as such.

— νNH_2 3,240—3,340 cm^{-1}
— $\nu\text{CH}=\text{CH}$ (benzene) 3,050 cm^{-1}
— νCO (amide) 1,650 cm^{-1}
— νCO (carbenzoxy) 1,730 cm^{-1}

c) N^1 -[carbenzoxy ($\pm$) leucyl]- N^2 -[5-nitro-2'-furylacrylidene]-hydrazine

To 14 g ($\frac{\text{mol}}{20} = 13.96$ g) of carbobenzoxy ($\pm$) leucyl hydrazide in 80 ml of

methanol are added 8.4 g ($\frac{\text{mol}}{20}$) of 5-nitro-2-furyl acrolein in 84 ml of tetrahydro-

furan. Crystals are produced before the addition is completed. Heating under reflux takes place for one hour, followed by concentration to half volume. At ambient temperature, ether is added, cooling takes place and there are obtained 10.9 g [yield = 88% (theoretical yield: 12.4 g)] of yellow solid, $Mp = 142-145^\circ \text{C}$.

After recrystallisation (ethanol) $Mp = 145.5-146^\circ \text{C}$.

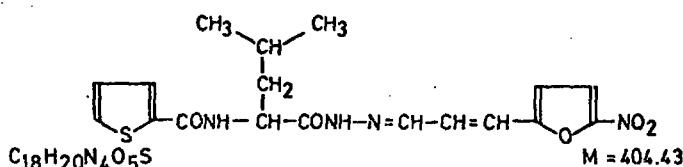
Analysis:

	C%	H%	N%
Calculated:	58.87	5.64	13.08
Found:	58.75	5.71	13.12

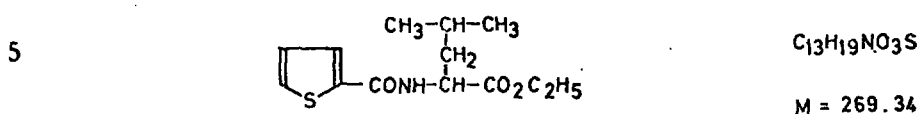
— νNH 3,320 cm^{-1}
— νCO 1,690 cm^{-1}
— νNO_2 1,520—1,550 cm^{-1}

Example 9.

$N^1[N'-(2'-\text{thenoyl}) (\pm) \text{leucyl}]-N^2-[5''\text{-nitro-2''-furylacrylidene}]-\text{hydrazine}$.



a) $N-(2\text{-thenoyl}) (\pm) \text{leucine ethyl ester}$:



Method A—

Starting from the free amino ester. Following the conditions of Example 4, with a yield of 67.6%, a product is obtained which distils, $Bp_{0.19} = 133-136^\circ \text{C}$., and then solidifies, $Mp = 62-64^\circ \text{C}$.

Method B—

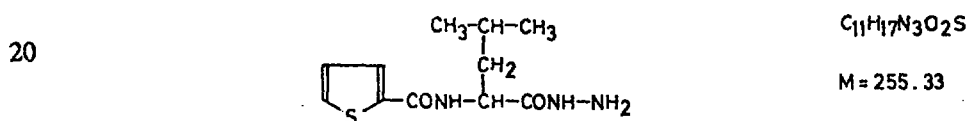
Starting from the hydrochloride of $(\pm) \text{leucine ethyl ester}$. Following the conditions of Example 4, with a yield of 89.4%, there is obtained a white solid of $Mp = 66-67^\circ \text{C}$.; the product distils, $Bp_{0.3} = 135-137^\circ \text{C}$.

Chromatography in vapour phase:

V.P.C. (column = S.E. 30; $T = 215^\circ \text{C}$.; $H_2 = 50 \text{ cc/min}$): purity = 100%

— νNH $3,300 \text{ cm}^{-1}$
 — $\nu\text{CH}=\text{CH}$ (thiophene) $3,100 \text{ cm}^{-1}$
 — νCO $1,720 \text{ cm}^{-1}$

b) $N^1-[N'-(2'-\text{thenoyl}) (\pm) \text{leucyl}]-\text{hydrazide}$:



The following are left at ambient temperature for 48 hours: 13.5 g ($\frac{\text{mol}}{20} =$

13.45 g) of $N-2\text{-thenoyl} (\pm) \text{leucine ethyl ester}$, 220 ml of ethanol, 10.2 g ($\frac{\text{mol}}{5} =$

10 g) of NH_2-NH_2 , 98% H_2O and 0.5 ml of acetic acid. By evaporation to dryness, an oily residue is obtained which, when ether is added, crystallises, yielding $10 \text{ g} = 79\%$ (theoretical yield: 12.7 g) of a solid melting at $145-147^\circ \text{C}$. After recrystallisation (ethanol) $Mp = 146-147^\circ \text{C}$.

Analysis:

	C%	H%	N%	S%
Calculated:	51.75	6.71	16.46	12.96
Found:	51.78	6.65	16.40	12.59

— νNH $3,200 \text{ cm}^{-1}$
 — $\nu\text{CH}=\text{CH}$ (thiophene) $3,120 \text{ cm}^{-1}$
 — νCO $1,660 \text{ cm}^{-1}$
 — $\nu\text{C}-\text{N}$ $1,370 \text{ cm}^{-1}$

c) N¹-[N'-(2'-thenoyl) (±) leucyl]-N²-[(5''-nitro-2''-furyl)-acrylidene]-hydrazine:

Following the conditions of Example 8 and starting with 6.4 g ($\frac{\text{mol}}{40} = 6.38 \text{ g}$)

of N¹-[N'-(2'-thenoyl) (±) leucyl]-hydrazide. After heating under reflux for 2 hours, concentration to half volume, adding ether and crystallising at ambient temperature, there is obtained a first cut of 5.5 g of a yellow solid, Mp=189—190° C., and a second cut of 2.7 g of yellow solid, Mp=177—179° C.

The second cut, recrystallised from methanol, yields 1.3 g of product, Mp=193—194° C. Yield 6.8 g=67.5% (theoretical yield: 10.1 g). After recrystallisation from methanol, Mp=194.5—195° C.

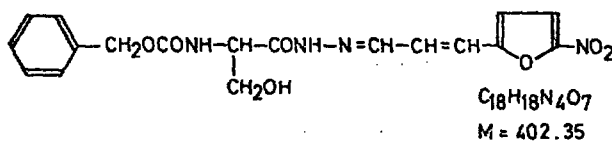
Analysis:

	C%	H%	N%	S%
Calculated:	53.46	4.98	13.86	7.92
Found:	53.50	5.01	13.79	8.00

— νNH	3,340 cm ⁻¹
— νCO (conjugated)	1,640 cm ⁻¹
— νCO	1,690 cm ⁻¹
— νNO ₂	1,520—1,540 cm ⁻¹

Example 10.

N¹-[N'-carbobenzoxy (±) seryl]-N²-[5'-nitro-2'-furylacrylidene]-hydrazine:



10 g ($\frac{\text{mol}}{25}$) of N-carbobenzoxy (±) seryl hydrazine are dissolved in 200 ml

of tepid methanol. 6.7 g ($\frac{\text{mol}}{25}$) of 5-nitro-2-furyl acrolein in 51 ml of tetrahydro-

furan are added at a temperature of 50° C. After heating under reflux for 2 hours, concentration to a third of the initial volume, addition of ether and after one night in the refrigerator, there are obtained 10.8 g=67.5% (theoretical yield=16 g) of a product melting at 150—151° C. After recrystallisation (ethanol), Mp=151—152° C.

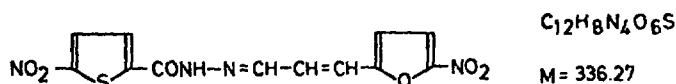
Analysis:

	C%	H%	N%
Calculated:	53.73	4.50	13.93
Found:	53.90	4.67	13.98

— νNH	3,420 cm ⁻¹
— νCO	1,700—1,730 cm ⁻¹
— νNO ₂	1,560 cm ⁻¹

Example 11.

N¹-[5'-nitro-2'-thenoyl]-N²-[5''-nitro-2''-furylacrylidene]-hydrazine:



a) Ethyl-5-nitro-2-thiophene carboxylate:



17.4 g ($\frac{\text{mol}}{10} = 17.31$ g) of 5-nitrothiophene carboxylic acid are dissolved in 85

ml of absolute ethanol. A stream of gaseous hydrochloric acid is caused to enter the boiling solution to the point of saturation, and for 5 hours. Evaporation to dryness takes place and then the solid residue is washed with a sodium bicarbonate solution. It is suction-filtered and washed with water. After drying, there are obtained 17.7 g of a yellow product with a melting point of 63—65° C. and the yield is 88% theoretical yield=88%).

The N¹-(5'-nitro-2'-thenoyl)-hydrazide is prepared by reacting hydrazine with ethyl 5-nitro-2-thiophene carboxylate. b) 6.3 g ($\frac{\text{mol}}{30} = 6.25$ g) of N¹-(5'-nitro-2-

thenoyl]-hydrazide are dissolved in 100 ml of dry tetrahydrofuran. 5.6 g ($\frac{\text{mol}}{30} =$

5.55 g) of 5-nitro-2-furyl acrolein in 56 ml of tetrahydrofuran are added. Heating under reflux takes place for one hour and, 25 minutes after starting the heating, crystallisation commences; the crystals are suction-filtered, washed with ether and dried. There are obtained 7.9 g (yield 70%—theoretical yield=11.2 g) of a yellow solid of Mp=235—236° C.

Recrystallisation (tepid dimethyl formamide+ether) leaves the melting point unchanged.

Analysis:

	C%	H%	N%	S%
Calculated:	42.85	2.40	16.66	9.53
Found:	42.87	2.37	16.58	9.45

Infra-red spectrum:

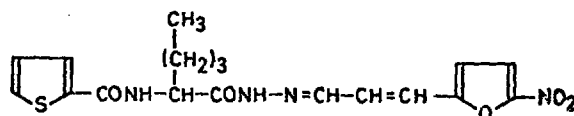
γ CO	1,650 cm ⁻¹
C—NO ₂	1,560 cm ⁻¹
C=N—	1,630 cm ⁻¹



1,030—1,075 cm⁻¹

Example 12.

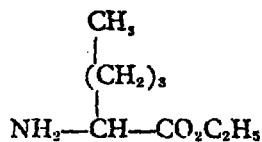
N¹-[(2'-thenoyl) Nor (±)leucyl]-N²-[5''-nitro-2''-furylacrylidene]-hydrazine.



C₁₈H₂₀N₄O₅S

M = 404.43

a) Nor (±) leucine ethyl ester:



C₈H₁₇NO₂

M=159.22

66 g ($\frac{\text{mol}}{2}$) of Nor (±) leucine are suspended in 375 ml of absolute ethanol.

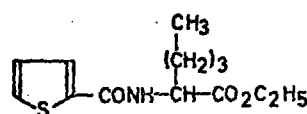
Hydrochloric acid gas is introduced into the mixture at boiling point for 6 hours (until saturation is reached). The substance is evaporated to dryness and then the treatment is repeated with fresh ethanol. After again being evaporated to dryness, the crude hydrochloride is treated with chloroform, saturated with NH₃. By distillation, there are

obtained 38.7 g of a colourless liquid of $Bp_{21}=102-103^{\circ}\text{C.}$; after redistillation $Bp_{18}=98-99^{\circ}\text{C.}$ V.P.C. = 100%.

Analysis:

	C%	H%	N%
Calculated:	60.34	10.76	8.80
Found:	60.30	10.80	8.75
γNH_2			3,300—3,400 cm^{-1}
CO			1,740 cm^{-1}
C			
O			
C			
			1,170 cm^{-1}

b) (N-2'-thenoyl)-Nor ($\pm$) leucine ethyl ester:



$\text{C}_{13}\text{H}_{10}\text{NO}_3\text{S}$

$M = 269.34$

15.9 g ($\frac{\text{mol}}{10}$) of Nor ($\pm$) leucine ethyl ester are dissolved in 50 ml of pyridine,

whereafter there are introduced 14.7 g ($\frac{\text{mol}}{10} = 14.65\text{ g}$) of 2-thiophene carboxylic

acid chloride. The mixture is left for one hour at ambient temperature and then it is poured into iced water. The oil which forms quickly crystallises. There are obtained 24 g of a light yellow product with a melting point of $80-81^{\circ}\text{C.}$, with a yield of 80.7% (theoretical yield = 26.9 g). After recrystallisation (ethyl acetate), the melting point is $81-82^{\circ}\text{C.}$

Analysis:

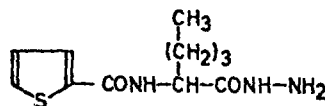
	C%	H%	N%	S%
Calculated:	57.97	7.11	5.20	11.90
Found:	57.91	7.12	5.21	12.01

γNH 3,340 cm^{-1}

CH=CH 3,100 cm^{-1}
CO (ester) = 1,760 cm^{-1}
CO (conjugated amide) = 1,640 cm^{-1}

C=C and 1,031 cm^{-1}
740 cm^{-1}

c) N^1 -[(2'-thenoyl) Nor ($\pm$) leucyl]-hydrazide.



$\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_2\text{S}$

$M = 255.33$

13.5 g ($\frac{\text{mol}}{20} = 13.45\text{ g}$) of N^1 -[2'-thenoyl]-Nor-($\pm$) leucine ethyl ester, 20 ml

of isopropanol, 10.2 g ($\frac{\text{mol}}{5} = 10\text{ g}$) of $\text{NH}_2\text{—NH}_2\text{.H}_2\text{O}$ (98%) and 0.5 ml of acetic acid are heated under reflux for 5 hours. The crude reaction mixture with

addition of ether yields 11.5 g of white crystals with a melting point of 116—118° C. Yield=90% (theoretical yield=12.8 g). After recrystallisation (isopropanol), the melting point is 127—128° C.

Analysis:

	C%	H%	N%	S%
Calculated:	51.75	6.71	16.46	12.96
Found:	51.77	6.69	16.47	12.54

5	ν NH	3,300 cm ⁻¹ (a single peak)	5
	CO (conjugated)	1,640 cm ⁻¹	
10	CO	1,670 cm ⁻¹	10

d) N¹-[(2'-thenoyl)-Nor-(±) leucyl]-N²-[5''nitro-2''furylacrylidene]-hydrazine:

8.5 g ($\frac{\text{mol}}{30}$) of N¹-[(2'-thenoyl)-Nor-(±) leucyl]-hydrazide in 180 ml of

methanol and 5.6 g ($\frac{\text{mol}}{30}$) of 5-nitro-2-furyl acrolein in 56 ml of tetrahydrofuran

are heated under reflux for 2 hours. After concentration to half volume, there are obtained, in two cuts: 7.7 g of product of melting point 188—192° C., yield=57.5% (theoretical yield=13.4 g).

After being recrystallised twice (ethyl acetate), the melting point is 200—201° C. (with decomposition).

Analysis:

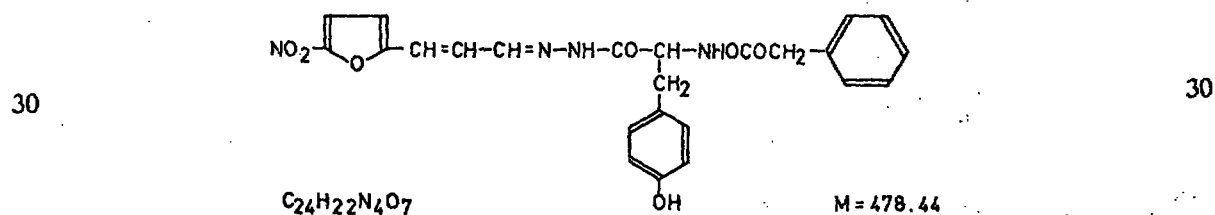
20	C%	H%	N%	S%	20
	Calculated:	53.46	4.98	13.86	7.92
	Found:	53.44	5.01	13.79	7.86

Infra-red spectrum:

25	γ NH	3,300 cm ⁻¹	25
	γ CO (conjugated)	1,640 cm ⁻¹	
	γ 	1,630 cm ⁻¹	
		1,020 cm ⁻¹	

Example 13.

N¹-[5'-nitro-2'-furylacrylidene]-N²-[(N''-carbobenzoxy) (±) tyrosyl]-hydrazine:



At 70° C., 11 g ($\frac{\text{mol}}{30}=10.97$ g) of (N''-carbobenzoxy) (±) tyrosyl)-hydrazide

are dissolved in 180 ml of ethylene glycol and then 5.6 g ($\frac{\text{mol}}{30}$) of 5-nitro-2-furyl

acrolein in 56 ml of tetrahydrofuran are introduced at a temperature of 60° C. Heating takes place for 2 hours at 60° C. and then water is added until clouding occurs. There is obtained an impure yellow solid, which is separated by filtering with suction. 16.3 g of product (theoretical yield=16.1 g) are obtained with a melting point of 123—125° C. After recrystallisation from 150 ml of methanol, a product with a melting point of 182—183° C. is obtained in a yield of 9.1 g=56.5% (theoretical yield=16.1 g). After a second recrystallisation from methanol, the melting point is 184—185° C.

Analysis:

	C%	H%	N%
Calculated:	60.24	4.64	11.70
Found:	60.20	4.63	11.66

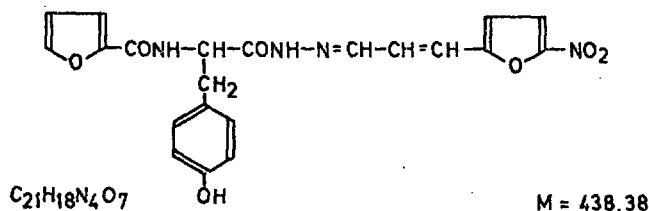
γ OH 3,600—3,400 cm^{-1} (large)
 NH 3,240 CO (amide) = 1,690 cm^{-1}
 CO = 1,740 cm^{-1} C—NO₂ = 1,520—1,550 cm^{-1}
 (carbobenzoxy)



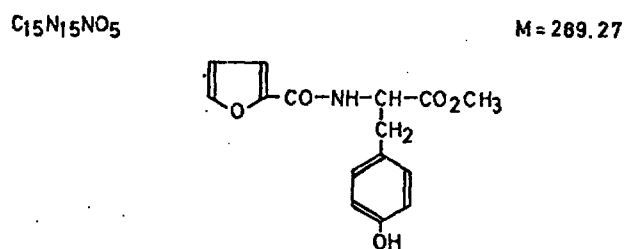
(C=C) 1,015—1,075 cm^{-1}

Example 14.

N¹-[N'-2'-furoyl ($\pm$) tyrosyl]-N²-[5''-nitro-2''-furylacrylidene]-hydrazine.



a) N-2'-furoyl ($\pm$) tyrosine methyl ester:



Between 0° and +5° C., 23.2 g ($\frac{\text{mol}}{10}$ = 23.16 g) of a hydrochloride of tyrosine methyl ester are dissolved in 100 ml of water which contain 33.5 g ($\frac{\text{mol}}{10}$) of NaHCO₃. While stirring, there are simultaneously added: 13 g ($\frac{\text{mol}}{10}$) of furoyl chloride and 8.5 g ($\frac{\text{mol}}{10}$) of NaHCO₃, in 85 ml of water. Heating takes place at 50° C. for one hour, the product is agglomerated and it solidifies when the heating is terminated. After filtering with suction and washing with water, there are obtained 24.6 g of a slightly coloured product which has a melting point of 117—119° C., the yield being 85.4% (theoretical yield 28.9 g). After recrystallisation (ethyl acetate+traces of hexane), the melting point is raised to 123—125° C.

Analysis:

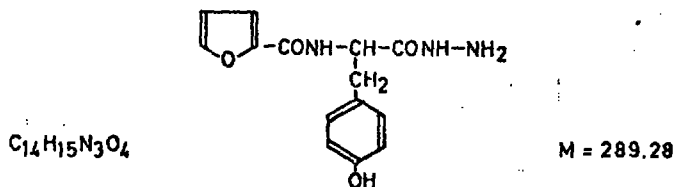
	C%	H%	N%
Calculated:	62.29	5.22	4.84
Found:	62.24	5.20	4.77

OH 3,680—3,400 cm^{-1} (large)
 CO (ester) 1,740 cm^{-1}
 CO (amide) 1,640 cm^{-1}
 conjugated)

R CO₂CH₃



745 cm^{-1}
 880 cm^{-1}
 1,020 cm^{-1}
 1,170 cm^{-1}

b) N¹-[N'-2'-furoyl (±) tyrosyl]-hydrazide:

The following are left at ambient temperature for 48 hours: 14.5 g ($\frac{\text{mol}}{20}$) of N-furoyl (±) tyrosine methyl ester in 220 ml of alcohol (to be made tepid for dissolving purposes), 10.2 g ($\frac{\text{mol}}{5}$) = 10 g of NH₂-NH₂ · 98% H₂O and 0.5 ml of acetic acid. Crystallisation occurs and, after being left for a short time in the refrigerator and adding ether, there are obtained by suction-filtering 10.2 g of white product, yield = 70.6% (theoretical yield = 14.45 g), with a melting point of 174—175° C. After recrystallisation from ethanol, the melting point is 175.5—176° C.

Analysis:

	C%	H%	N%
Calculated:	58.12	5.22	14.52
Found:	58.10	5.30	14.48

ν OH =	3,600—3,400 cm ⁻¹
NH =	3,300 cm ⁻¹
CO (conjugated)	1,650 cm ⁻¹

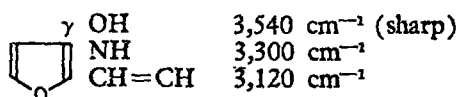
c) N¹-[N'-2'-furoyl (±) tyrosyl]-N²-[5''nitro-2''-furylacrylidene]-hydrazine:

At the temperature of 60° C., 14.5 g ($\frac{\text{mol}}{20}$) of N¹-[N'-2'-furoyl (± tyrosyl)]-hydrazide are dissolved in 320 ml of ethylene glycol. At a temperature lower than 60° C., 8.4 g ($\frac{\text{mol}}{20}$) of 5-nitro-2-furyl acrolein in 84 ml of tetrahydrofuran are introduced thereinto. After heating at 80° C. for 4 hours, the tetrahydrofuran is evaporated under vacuum.

By filtering with suction (difficult) and after washing with water, a yellow solid is separated which has a melting point of 192—194° C. After recrystallisation (water-dimethylformamide 1:1), Mp = 229—230° C., yield = 12.4 g = 57% (theoretical yield = 21.6 g).

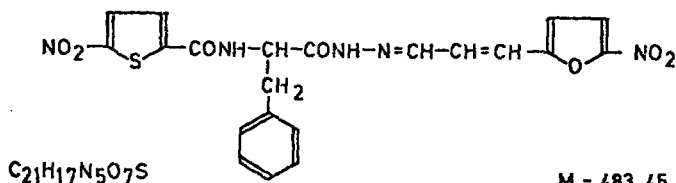
Analysis:

	C%	H%	N%
Calculated:	57.55	4.13	12.77
Found:	57.53	4.14	12.79

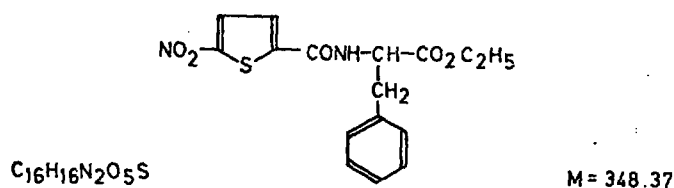


CO =	1,680 cm ⁻¹
CO (conjugated) =	1,650 cm ⁻¹
	1,020 cm ⁻¹
	1,080 cm ⁻¹
	750 cm ⁻¹
	880 cm ⁻¹

Example 15.
 N^1 -[N' -(5'-nitro-2'-thenoyl ($\pm$) phenylalanyl]- N^2 -[5''-nitro-2''-furylacrylidene]-hydrazine.



a) N -[5'-nitro-2'-thenoyl ($\pm$) phenyl alanine ethyl ester:



19.3 g ($\frac{\text{mol}}{10}$) of ($\pm$) phenyl alanine ethyl ester are dissolved in 150 ml of pyridine. 19.2 g ($\frac{\text{mol}}{10} = 19.15$ g) of 5-nitro-2-thienoyl chloride are added in small portions. After stirring at ambient temperature for one hour, cooling in iced water, filtering with suction and washing with water, there are isolated 29 g of a product having a melting point of 150—151° C., with a yield of 83.5% (theoretical yield = 34.8 g).

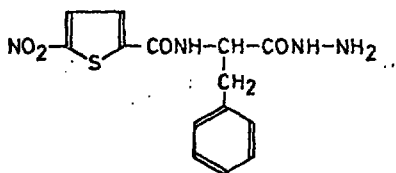
After recrystallisation from ethanol, the melting point is 150—151° C.

Analysis:

	C%	H%	N%	S%
Calculated:	55.16	4.63	8.04	9.20
Found:	55.18	4.59	8.02	9.22

ν NH 3,300 cm^{-1} C—NO₂ 1,560 cm^{-1}
 CO (ester) 1,740—1,750 cm^{-1} (split up)
 CO (conjugated amide) 1,630 cm^{-1}

b) N^1 -[N' -(5'-nitro-2'-thenoyl ($\pm$) phenylalanyl]-hydrazide:
 $C_{14}H_{14}N_4O_4S$ $M = 334.34$



20.8 g ($\frac{\text{mol}}{16.7}$) of N -(5'-nitro-2'-thenoyl) ($\pm$) phenyl alanine ethyl ester are dis-

solved in 175 ml of tetrahydrofuran and 175 ml of methanol. 9.2 g ($\frac{\text{mol}}{5.55} = 9$ g) of 98% hydrazine hydrate in solution in 30 ml of methanol are then introduced slowly at ambient temperature (in about 1 hour). The solution is left at ambient temperature for 48 hours and is then heated under reflux for 1 hour. After concentration to half volume, followed by adding ether, there is isolated a first cut of 11 g of yellow product

of melting point 190—192° C. and a second cut of 3.4 g of yellow product of melting point=180—185° C. After recrystallisation of the 14.4 g from 650 ml of ethanol, 8 g, yield=40% (theoretical yield=20 g) of yellow product of Mp=206—208- C. are obtained, and following a second recrystallisation from ethanol, the melting point is 214—216° C.

Analysis:

	C%	H%	N%	S%
Calculated:	50.29	4.20	16.76	9.61
Found:	50.27	4.18	16.79	9.64

c) N¹-[N'-(5'-nitro-2'-thenoyl) (±) phenylalanyl]-N²-[5''-nitro-2''-furylacrylidene]-hydrazine:

10.1 g ($\frac{\text{mol}}{33}$) of N¹-[N'-(5'-nitro-2'-thenoyl) (±) phenylalanyl]-hydrazine are

dissolved at boiling point in 280 ml of tetrahydrofuran. 4.9 g ($\frac{\text{mol}}{33}$) of 5-nitro-2-furyl acrolein in 49 ml of tetrahydrofuran are added dropwise thereto.

After heating for 2 hours under reflux, evaporation to dryness is effected and the ether is recovered. There are isolated 13 g of yellow product having a melting point of 131—133° C. with a yield of 89% (theoretical yield 14.6 g). After recrystallisation (ethanol-dimethyl formamide 1:1 and traces of water), the melting point becomes 221.5—222° C.

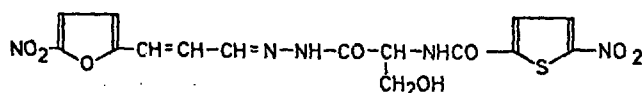
Analysis:

	C%	H%	N%	S%
Calculated:	52.18	3.54	14.49	6.63
Found:	52.20	3.57	14.50	6.62

ν NH 3,280 cm⁻¹ C—NO₂ 1,540—1,550 cm⁻¹
CO 1,680 cm⁻¹
CO (conjugated) 1,630 cm⁻¹

Example 16.

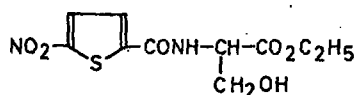
N¹-[(5'-nitro-2'-furylacrylidene)-N²-(N'-5''nitro-2''-thenoyl) (±) seryl]-hydrazine:



C₁₅H₁₃N₅O₈S

M = 423.35

a) N-(5'-nitro-2'-thenoyl) (±) serine ethyl ester:



C₁₀H₁₂N₂O₆S

M = 288.28

33.8 g ($\frac{\text{mol}}{5}$) of (±) serine ethyl ester hydrochloride are dissolved at about 0° in

100 ml of water containing 33.5 g ($\frac{\text{mol}}{2.5}$) of dry NaHCO₃. There are simultaneously added, while stirring, 38.4 g ($\frac{\text{mol}}{5}$) of 5-nitro-2-thienoyl chloride and 85 ml of an

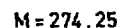
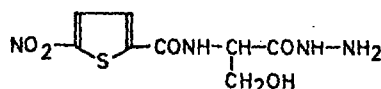
aqueous solution of 16.7 g ($\frac{\text{mol}}{5}$) of NaHCO_3 . After heating at 50°C . for one hour, washing with water and drying, there are isolated 39.3 g of crystalline product having a melting point of $112\text{--}115^\circ \text{C}$.; yield=68% (theoretical yield=57.6 g). The mother liquors, acidulated, yield 4.2 g of white product with a melting point of $154\text{--}156^\circ \text{C}$., which does not contain any alcohol or amine function.

The main product, recrystallised from ethanol, has a melting point of $126\text{--}127^\circ \text{C}$.

Analysis:

	C%	H%	N%	S%
Calculated:	41.66	4.19	9.71	11.12
Found:	41.68	4.20	9.69	11.14
Infra-red ν OH			3,550 cm^{-1}	
 NH			3,540 cm^{-1}	
 CH=CH			3,100 cm^{-1}	
			1,730 cm^{-1}	
 CO			1,540 cm^{-1}	
 C-NO ₂			1,040 cm^{-1}	
 C=C				

b) N^1 -[5'-nitro-2'-thenoyl ($\pm$) seryl]-hydrazide:



14.4 g ($\frac{\text{mol}}{20}$) of N^1 -(5'-nitro-2'-thenoyl) ($\pm$) serine ethyl ester are dissolved in 200 ml of methanol. At a temperature of 5°C ., 7.7 g ($\frac{\text{mol}}{6.66}$) of NH_2NH_2 . 98% H_2O in 24 ml of methanol are very slowly added.

After the addition, the mixture is cooled to 0°C . and stirring is continued for 2 hours. The mixture is left at ambient temperature for 48 hours. After filtering with suction and washing with ether, there are isolated 13.1 g=95.6% (theoretical yield=13.7 g) of a product melting at 189°C . After recrystallisation from water, the melting point is 190°C . (with decomposition).

Analysis:

	C%	H%	N%	S%
Calculated:	35.03	3.67	20.47	11.69
Found:	35.05	3.69	20.50	11.79
ν OH	3,600—3,400 cm^{-1}		CO (conjugated)	1,640 cm^{-1}
NH	3,300 cm^{-1}			
CO	1,670 cm^{-1}			

c) N^1 -[(5'-nitro-2'-furylacrylidene)- N^2 -(N^1 -5''-nitro-2''-thenoyl) ($\pm$) seryl]-hydrazine:

9.2 g ($\frac{\text{mol}}{30}$) of N^1 -[5'-nitro-2'-thenoyl ($\pm$) seryl]-hydrazide are dissolved at 60°C . in 210 ml of ethylene glycol. 5.6 g ($\frac{\text{mol}}{30}$) of 5-nitro-2-furylacrolcin in

56 ml of tetrahydrofuran are added to the solution. After heating for 2 hours at 60° C., the tetrahydrofuran is driven off under vacuum and water is added to the residue. 12.1 g of product crystallises, this product melting at 217° C. with decomposition. Yield=85% (theoretical yield=14.1 g). After recrystallisation from ethyl acetate—dimethyl formamide (2:1), the melting point is 217° C. (with decomposition).

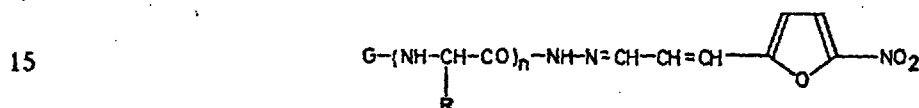
Analysis:

	C%	H%	N%	S%
Calculated:	42.56	3.09	16.55	7.57
Found:	42.58	3.13	16.50	7.60

10	ν OH	3,520 cm^{-1}	CO	1,700 cm^{-1}	C=N	1,630 cm^{-1}	10
	NH	3,320 cm^{-1}	CO	1,650 cm^{-1}	C—NO ₂	1,540 cm^{-1}	
				(conjugated)			

WHAT WE CLAIM IS:—

1. Nitrofurans represented by the general formula:



wherein

n is 0 or 1;

G is a furoyl, thenoyl, nitrothenoyl or carbobenzyloxy radical; and

20 R is hydrogen or a methyl, n-butyl, isobutyl, hydroxymethyl, benzyl, *p*-hydroxybenzyl or δ -(2-furoyl)-aminobutyl radical.

2. Nitrofurans as claimed in claim 1, wherein G is 2-thenoyl or 5-nitro-2-thenoyl.

3. [N¹-(5'-nitro-2'-thenoyl)-N²-(5''-nitro-2''-furylacrylidene)]-hydrazine.

25 4. [N¹-(5'-nitro-2'-thenoyl-glycyl)-N²-(5''-nitro-2''-furyl-acrylidene)]-hydrazine.

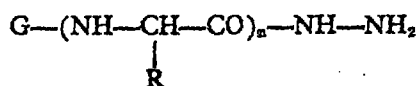
5. A pharmaceutical composition comprising, as an essential active ingredient, a compound as claimed in claim 1, 2, 3 or 4, in association with a pharmaceutical carrier or excipient therefor.

6. A pharmaceutical composition as claimed in claim 5, made up in a dosage unit form appropriate to the desired mode of administration.

30 7. A pharmaceutical composition as claimed in claim 5 or 6, the composition being in a form suitable for oral administration.

8. A pharmaceutical composition as claimed in claim 5, the composition being in a form suitable for topical administration.

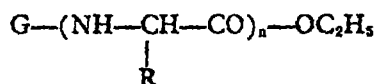
35 9. Process for preparing a nitrofurans derivative as claimed in claim 1, which comprises reacting 5-nitro-2-furyl-acrolein with a substituted hydrazine represented by the general formula:



wherein n , G and R have the same meanings as in claim 1, to obtain the required nitrofurans derivative.

40 10. Process according to claim 9, wherein the reaction is carried out in an organic solvent medium.

11. Process according to claim 9 or 10, wherein the substituted hydrazine is prepared by reacting hydrazine with an ester represented by the general formula:



45 wherein n , G and R have the same meanings as in claim 1.

12. Process according to claim 11, wherein the reaction is effected in the presence of an acid as catalyst.



56 ml of tetrahydrofuran are added to the solution. After heating for 2 hours at 60° C., the tetrahydrofuran is driven off under vacuum and water is added to the residue. 12.1 g of product crystallises, this product melting at 217° C. with decomposition. Yield=85% (theoretical yield=14.1 g). After recrystallisation from ethyl acetate—dimethyl formamide (2:1), the melting point is 217° C. (with decomposition).

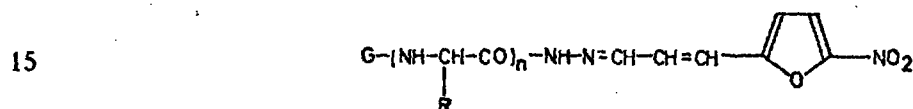
Analysis:

	C%	H%	N%	S%
Calculated:	42.56	3.09	16.55	7.57
Found:	42.58	3.13	16.50	7.60

10	ν OH	3,520 cm^{-1}	CO	1,700 cm^{-1}	C=N	1,630 cm^{-1}	10
	NH	3,320 cm^{-1}	CO	1,650 cm^{-1}	C—NO ₂	1,540 cm^{-1}	
				(conjugated)			

WHAT WE CLAIM IS:—

1. Nitrofurans derivatives represented by the general formula:



wherein

n is 0 or 1;

G is a furoyl, thenoyl, nitrothenoyl or carbobenzyloxy radical; and

20 R is hydrogen or a methyl, n-butyl, isobutyl, hydroxymethyl, benzyl, *p*-hydroxy-benzyl or δ -(2-furoyl)-aminobutyl radical.

2. Nitrofurans derivatives as claimed in claim 1, wherein G is 2-thenoyl or 5-nitro-2-thenoyl.

3. [N¹-(5'-nitro-2'-thenoyl)-N²-(5''-nitro-2''-furylacrylidene)]-hydrazine.

4. [N¹-(5'-nitro-2'-thenoyl-glycyl)-N²-(5''-nitro-2''-furyl-acrylidene)]-hydrazine.

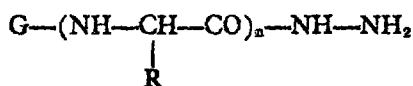
25 5. A pharmaceutical composition comprising, as an essential active ingredient, a compound as claimed in claim 1, 2, 3 or 4, in association with a pharmaceutical carrier or excipient therefor.

6. A pharmaceutical composition as claimed in claim 5, made up in a dosage unit form appropriate to the desired mode of administration.

30 7. A pharmaceutical composition as claimed in claim 5 or 6, the composition being in a form suitable for oral administration.

8. A pharmaceutical composition as claimed in claim 5, the composition being in a form suitable for topical administration.

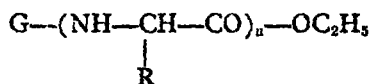
35 9. Process for preparing a nitrofurans derivative as claimed in claim 1, which comprises reacting 5-nitro-2-furyl-acrolein with a substituted hydrazine represented by the general formula:



wherein n , G and R have the same meanings as in claim 1, to obtain the required nitrofurans derivative.

40 10. Process according to claim 9, wherein the reaction is carried out in an organic solvent medium.

11. Process according to claim 9 or 10, wherein the substituted hydrazine is prepared by reacting hydrazine with an ester represented by the general formula:



45 wherein n , G and R have the same meanings as in claim 1.

12. Process according to claim 11, wherein the reaction is effected in the presence of an acid as catalyst.

C.,
ie.
in.

13. Process according to claim 12, wherein the acid is acetic acid.
14. Process for preparing a nitrofur derivative as claimed in claim 1, substantially as described in any one of the foregoing Examples 2 to 16.

HASELTINE, LAKE & CO.,

Chartered Patent Agents,

28, Southampton Buildings, Chancery Lane, London, WC2A 1AT,
Agents for the Applicants.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1974.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained



* C L M S *